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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/728,446	11/30/2000	Glenn Friedrich	LEX-0101-USA	6090

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EXAMINER
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ART UNIT	PAPER NUMBER
1637	12

DATE MAILED: 10/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	09/728,446	FRIEDRICH ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *19 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group IV in Paper No. 11 is acknowledged.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

1. Claims 8 and 9 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a an embryonic stem cell line with a mutation in a gene which encodes SEQ ID NO: 819.

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the proteins. The cited utilities identified in the specification are to detect the nucleic acid itself either as a hybridization probe or on a microarray. These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the protein. No well established utilities for this specific SEQ ID NO: 819 are identified in either the specification or in the cited prior art.

Substantial utility

Given the absence of a well established utility, the next issue is whether substantial utilities are disclosed in the specification. Here, there is no evidence (in the form of published prior art) which supports a substantial utility. The sequence is not known in the prior art and the gene from which sequence is derived is not known in the prior art. Further, the specification identifies no utility which is substantial regarding this sequence.

As noted in the utility guidelines, methods of treating unspecified diseases, basic research on a product to identify properties, intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials). The claim to a cell which comprises a mutation in a particular sequence, where there is no particular mutation claimed does not support a substantial utility for an unknown protein with unknown function. Further, where no association has been made between the gene or sequence and any particular phenotype or disease state, the specification does not support a substantial utility for this unknown SEQ ID NO: 819 with unknown function which is not associated with any disease.

Specific Utility

In the current case, there is no specific utility because the use of the claimed nucleic acid is not particular to the sequence being claimed. Any asserted utility would be applicable to the general class of cDNAs. Any partial nucleic acid prepared from any cDNA may be used to as a probe in the preparation and or identification of a full-length cDNA and may be used as a target to engineer mutations in cells which comprise the

gene. As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed". Here, there is no disclosure of any condition which can be diagnosed and hence, no specific utility. A starting material that can only be used to produce a final product does not have a substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In this case the embryonic stem cell line that is to be produced as final products resulting from processes involving the claimed SEQ ID NO: 819 has no identified specific and substantial utilities.The research contemplated by Applicants to characterize potential embryonic stem cell lines, especially their biological activities,does not constitute a specific and substantial utility. Identifying and studying the properties of the cell line itself does not define a "real world" context of use. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the cDNA compounds such that another non-asserted utility would be well established for the compounds.

Finally, with regard to the utility analysis, the current situation directly tracks Example 9 of the utility guidelines, where an unknown nucleic acid fragment of entirely unknown function was characterized as lacking utility.

Claim Rejections - 35 USC § 112 - Description

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which are different from those disclosed in the specification. The specific Genus here is all cell lines which have a mutation in SEQ ID NO: 819. Since SEQ ID NO: 819 is 349 nucleotides in length, this size of this genus is 3^{349} or 3.2×10^{166} (Actually, this amazingly large number is an underestimate because it simply calculates the number of possible different single base pair changes. The number of possible mutations, when including insertions, deletions or other variations would be significantly larger). This large genus is represented in the specification by only the particularly named SEQ ID Nos. Thus, applicant has express possession of only one sequence, SEQ ID NO: 819 in a genus which comprises many hundreds of trillions of different possibilities. Here, no common

element or attributes of the sequences are disclosed, not even the presence of certain domains. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations is provided.

Further, these claims encompass full length genes when only a small portion of a gene is provided, as well as allelic variants including insertions and mutations. No written description of alleles, of upstream or downstream regions containing additional sequence, or of alternative splice variants has been provided in the specification.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of mutations in SEQ ID NO: 819, without any specific structure, is precisely the situation of naming a type of material which is generally known to likely be capable of being made, but, except for the known

sequence, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a deletion, without any structural definition of the particular deletions claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise deletions of SEQ ID NO: 819. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 112 - Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to an isolated embryonic stem cell line which comprises mutations in a gene which comprises SEQ ID NO: 819 where the gene is unknown, the mutations are unknown and any phenotype resulting from the gene and mutation are unknown. The invention is is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass any embryonic stem cell line which has any mutation in a gene which encodes SEQ ID NO: 819. Because the nature of the mutation is not specifically defined, a complete deletion of SEQ ID NO 819 and replacement with some other sequence would be permitted by the claim. The claims are broadly drawn with no specific function, no specific phenotype, no specific result and no specifics associated with this stem cell line. Thus, there are no specific uses attached to this stem cell line, so it is broadly open to any use whatsoever.

Quantity of Experimenation

The quantity of experimentation in this area is large since there is significant variability in the effect of mutations on cells. In particular, prior to any experiments being performed, it would be necessary to determine what gene is associated with SEQ ID NO: 819, something which the applicant was unable to perform as of the filing date. After determination of the gene associated SEQ ID NO: 819, it would be necessary to determine the function of that gene in it's native environment. Following that, analysis of mutations in the particular cell type claimed, embryonic stem cells would be necessary to determine the effect of any of a immense number of undefined changes upon the embryonic stem cells. Even then, there would be no real world use associated with the stem cells unless by chance, some unpredictable association was found between the gene or a mutation of gene and some phenotype. Each of these steps represents unpredictable and difficult undertakings in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The prior art teaches that association of genes and effects is unpredictable. For example, Reymond et al (Genomics (2002), 79(6), 824-832) teaches "This study underscored the limitations of in-silico-only gene prediction, as many PREDs were incorrectly predicted (abstract)." Here, Reymond is teaching that the invention cannot predictably rely upon association of sequences with genes predicted to exist in silico, because those genes may not, in fact, be correct themselves. Further, even if a gene is identified, without specific information regarding the genes function, it is entirely unpredictable what effects alterations on that gene will have. Ito et al (PNAS, (2001 Apr 10) 98 (8) 4569-74) notes that the databases are "flooded with novel genes of unpredictable functions (abstract)". Ito expressly proves the unpredictability of gene function. Even where there is some specific information to design a knockout mouse, however, the specific effect may not always be predictable. As Couse et al (Endocrine Reviews, (1999 Jun) 20 (3) 358-417) notes, "Upon the successful generation of a knockout, confirmatory studies are undertaken to corroborate previously established hypotheses of the function of the disrupted gene product. As these studies continue, observations of unpredicted phenotypes or, more likely, the lack of a phenotype that was expected based on models put forth from past investigations are noted. Often the surprising phenotype is due to the loss of a gene product that is downstream from the functions of the disrupted gene, whereas the lack of an expected phenotype may be due to compensatory roles filled by alternate mechanisms (see page 404, column 1)." Thus, Couse expressly shows that even when a knockout is made, with a particular predicted phenotype based upon a gene product, it is unpredictable what actual phenotype will result. Thus, given the absence of any information regarding the use of SEQ ID NO: 819 and any information regarding predicted phenotypes, the teaching of

the prior art strongly supports the unpredictable nature of the use of SEQ ID NO: 819 in an embryonic stem cell.

Working Examples

The specification has one working example, but the working example was not checked to determine whether it has any particular phenotype.

Guidance in the Specification.

The specification has no guidance on how to use the embryonic stem cell line which comprises a mutation in SEQ ID NO: 819 for any purpose other than further research on the embryonic stem cell line itself, to determine if it has any function.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability is high and the prior art teaches such unpredictability. The specification provides one with no written description or guidance that leads one to a reliable method of using the embryonic stem cell lines with SEQ ID NO: 819 mutations for any purpose whatsoever. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art recognized problems in the use of knockout cell lines in a predictable way as discussed by Couse. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large

quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to use the product of the claims as broadly written.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

October 25, 2002